Guidance for Industry

Changes to an Approved NDA or ANDA

DRAFT GUIDANCE

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For questions on the content of the draft document contact Nancy Sager, 301-594-5633 (CDER).

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 1999
CMC #

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Draft — Not for Implementation

GUIDANCE FOR INDUSTRY[1]

Changes to an Approved NDA or ANDA

(Due to the complexity of this draft document, please identify specific comments by line number. Use the pdf version of the document whenever possible)

I. INTRODUCTION

On November 21, 1997, the President signed the Food and Drug Administration Modernization Act (the Modernization Act).[2] Section 116 of the Modernization Act amended the Food, Drug, and Cosmetic Act (the Act) by adding section 506A (21 U.S.C. 356a), which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such change. The Food and Drug Administration (FDA) is proposing to amend its regulations on supplements and other changes to an approved application (21 CFR 314.70) to conform to section 506A of the Act.

The purpose of this draft guidance is to provide recommendations to holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) who intend to make postapproval changes in accordance with Section 506A and the proposed amended regulations at 21 CFR 314.70. The guidance covers recommended reporting categories for postapproval changes for drugs, other than specified biotechnology and specified synthetic biological products. Recommendations are provided for postapproval changes in: (1) components and composition, (2) sites, (3) manufacturing process, (4) specification(s), (5) package, (6) labeling, and (7) miscellaneous changes. This draft guidance document, which cites proposed 21 CFR 314.70, will be revised based on public comments and implemented for use as a companion document when 21 CFR 314.70 is finalized.

Recommendations on reporting categories for changes relating to specified biotechnology and

[1] This guidance has been prepared under the direction of the Chemistry, Manufacturing and Controls Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on the reporting categories for manufacturing changes to approved NDAs and ANDAs. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

[2] Pub. L. 105-115.

specified synthetic biological products regulated by CDER are found in the guidance for industry entitled *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997).[3]

This guidance does not provide recommendations on the specific information that should be developed by an applicant to validate the effect of the change on the identity, strength (e.g., assay, content uniformity), quality (e.g., physical, chemical, and biological properties), purity (e.g., impurities and degradation products), or potency (e.g., biological activity, bioavailability, bioequivalence) of a product as they may relate to the safety or effectiveness of the product. CDER has published guidances, including the SUPAC (Scale-up and Postapproval Changes) guidances, that provide recommendations on reporting categories and/or the type of information that should be developed by the applicant to validate the effect of the change on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product. To the extent that the recommendations on reporting categories in this guidance, when finalized, are found to be inconsistent with prior published guidance, such as the SUPACs, the recommended reporting categories in such prior guidance will be superseded by this guidance. CDER intends to update the prior published guidances to make them consistent with this guidance. An applicant should consider all relevant CDER guidance documents for recommendations on the information that should be submitted to support a given change. If guidance for either recommended filing categories and/or information that should be submitted to support a particular change is not available, the appropriate CDER chemistry or microbiology review staff should be consulted.

II. REPORTING CATEGORIES

FDA's proposed amended regulations at 21 CFR 314.70 provide for three categories of change: major, moderate, and minor. These types of changes are distinguished in the following paragraphs. Citations are to the proposed rule.

A ***major change*** is a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product. A major change requires the submission of a supplement and approval by FDA prior to distribution of the product made using the change. This type of supplement is called and should be clearly labeled a ***Prior Approval Supplement*** (21 CFR 314.70(b)). An applicant may ask FDA to expedite its review of a prior approval supplement for public health reasons (e.g., drug shortage) or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. This type of supplement is called and should be clearly labeled a ***Prior Approval Supplement-Expedited Review Requested*** (21 CFR

[3] FDA is currently revising the 1997 guidance and intends to issue it in draft for public comment.

314.70(b)(4)).[4] Requests for expedited review based on extraordinary hardship should be reserved for manufacturing changes made necessary by catastrophic events (e.g., fire) or by events that could not be reasonably foreseen and for which the applicant could not plan.

A ***moderate change*** is a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. A moderate change requires the submission of a supplement to FDA at least 30 days before the distribution of the product made using the change. This type of supplement is called and should be clearly labeled a ***Supplement--Changes Being Effected in 30 Days*** (21 CFR 314.70(c)(3)). The product made using a moderate change can not be distributed if FDA informs the applicant within 30 days of receipt of the supplement that a prior approval supplement is required (21 CFR 314.70(c)(5)(i)). Also, if FDA informs the applicant within 30 days of receipt of the supplement that information required under 21 CFR 314.70(c)(4) is missing, distribution must be delayed until the missing information is provided and FDA determines that the additional information is in compliance with this section of the regulations (21 CFR 314.70(c)(5)(ii)). FDA may identify certain moderate changes for which distribution can occur when FDA receives the supplement (21 CFR 314.70(c)(6)). This type of supplement is called and should be clearly labeled a ***Supplement--Changes Being Effected***. If after review FDA disapproves a changes being effected in 30 days supplement or changes being effected supplement, FDA may order the manufacturer to cease distribution of the drugs that have been made using the disapproved change (21 CFR 314.70(c)(7)).

A ***minor change*** is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. The applicant must describe minor changes in its next ***Annual Report*** (21 CFR 314.70(d)).

Under 21 CFR 314.70(e), an applicant may submit one or more protocols (i.e., comparability protocols) describing tests, validation studies, and acceptable limits to be achieved to demonstrate the absence of an adverse effect from specified types of changes. A comparability protocol can be used to reduce the reporting category for specified changes. A proposed comparability protocol must be submitted as a prior approval supplement (21 CFR 314.70(e)). FDA intends to issue separate guidance(s) on comparability protocols.

III. GENERAL REQUIREMENTS

[4]Policies and procedures relating to requests for expedited review of supplements to approved ANDAs are documented in MAPP 5240.1 which can be located on the Internet at http://www.fda.gov/cder/mapp.htm.
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An applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully (21 CFR 314.70(a)(1)). **The applicant must list all changes included in the supplement or annual report in the cover letter (21 CFR 314.70(a)(6)).**

An applicant making a change to an approved application pursuant to 21 CFR 314.70 must also conform to other applicable laws and regulations, including current good manufacturing practice (CGMP) requirements of the Act (21 U.S.C. 351(a)(2)(B)) and applicable regulations in Title 21 of the *Code of Federal Regulations* (e.g., 210, 211, 314). For example, manufacturers must comply with the record-keeping requirements and ensure that relevant records are readily available for examination by authorized FDA personnel during an inspection and comply with relevant CGMP validation requirements.

A changes being effected supplement for labeling changes must include 12 copies of final printed labeling (21 CFR 314.70(c)(1)). Also, an applicant must promptly revise all promotional labeling and drug advertising to make it consistent with any labeling change implemented in accordance with the regulations (21 CFR 314.70(a)(4)).

Except for a supplemental application providing for a change in labeling, an applicant must include a statement in a supplemental application certifying that a field copy of the supplement has been provided to the applicant's FDA district home office (21 CFR 314.70(a)(5)).

IV. ASSESSING THE EFFECT OF MANUFACTURING CHANGES

A. Validate the Effects of the Change[5]

A drug made with a manufacturing change, whether a major manufacturing change or otherwise, may be distributed only after the holder validates the effects of the change on the identity, strength, quality, purity, and potency of the product as these factors may relate to the safety or effectiveness of the product (21 CFR 314.70(a)(2)). For each change, the supplement or annual report must contain information determined to be appropriate by FDA and include the information developed by the applicant in validating (assessing) the effects of the change (section 506A of the Act). The type of information

[5] *Validate the effects of the change* means to assess the effect of a manufacturing change on the identity, strength, quality, purity, or potency of a drug as these factors relate to the safety or effectiveness of the drug (21 CFR 314.3). The term validate or validation, as used in this guidance, is not the same as CGMP validation. Unless otherwise specified by FDA, CGMP validation (e.g., process, equipment) data need not be filed in the application but should be retained at the facility and be available for review by FDA at its discretion. Some CGMP validation information, in addition to the information validating the effects of the change specified in 506A(b) of the Act, should be submitted in an NDA or ANDA (e.g., sterilization process validation).

that should be included in a supplemental application or annual report is specified in 21 CFR 314.70(b)(3), (c)(4), and (d)(3).

1. Conformance to Specifications

An assessment of the effect of a change on the identity, strength, quality, purity, or potency of the drug product should include a determination that the drug substance intermediates, drug substance, in-process materials and/or drug product affected by the change conform to the approved specifications[6]. A *specification* is a quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components, including container closure systems, and in-process materials (21 CFR 314.3). For the purpose of defining specification in 21 CFR 314.3, *acceptance criteria* are numerical limits, ranges, or other criteria for the tests described (21 CFR 314.3). Conformance to a specification means that the material, when tested according to the analytical procedures listed in the specification, will meet the listed acceptance criteria.

2. Additional Testing

In addition to confirmation that the material affected by the manufacturing change(s) continues to meet its specification, the applicant should perform additional testing, when appropriate, to assess whether the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product have been affected. The assessment should include, as appropriate, evaluation of any changes in the chemical, physical, microbiological, biological, bioavailability and/or stability profiles. This additional assessment could involve testing of the postchange drug product itself or, if appropriate, the component directly affected by the change. The type of additional testing that an applicant should perform would depend on the type of manufacturing change, the type of drug substance and/or drug product, and the effect of the change on the quality of the product. For example, evaluation of changes in the impurity or degradant profile could first involve profiling by high pressure liquid chromatography (HPLC) and then, depending on the observed changes in the impurity profile, toxicology tests to qualify a new impurity or degradant or to qualify an impurity that is above a previously qualified level. Assessment of the effect of a change on bioequivalence when required under 21 CFR part 320 could

[6] If a specification needs to be revised as a result of the change, this would be considered a multiple change (See Sections VIII and XII).

include for example, multipoint and/or multimedia dissolution profiling and/or an in vivo bioequivalence study.

An applicant should consider all relevant FDA guidance documents for recommendations on the information that should be submitted to support a given change. If guidance for information that should be submitted to support a particular change is not available, the appropriate CDER chemistry or microbiology review staff should be consulted.

B. Equivalence

When testing is performed, the applicant should usually assess the extent to which the manufacturing change has affected the identity, strength, quality, purity, or potency of the drug product. Typically this is accomplished by comparing test results from pre- and postchange material and determining if the test results are equivalent. Simply stated -- is the product made after the change equivalent to the product made before the change? An exception to this general approach is when redocumentation of bioequivalence should occur for certain ANDA postapproval changes, the prechange material selected for comparison should be the reference listed drug. Equivalence comparisons frequently require a criterion for comparison with calculation of confidence intervals relative to a predetermined equivalence interval. For this, as well as for other reasons, *equivalence* does not necessarily mean identical. Equivalence may also relate to maintenance of a quality characteristic (e.g., stability) rather than a single test of an attribute.

C. Adverse Effect

Sometimes manufacturing changes have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. In many cases the applicant chooses not to implement these manufacturing changes, but sometimes the applicant wishes to do so. If an assessment concludes that a change has adversely affected the identity, strength, quality, purity, or potency of the drug product, **the change should be filed in a prior approval supplement, regardless of the recommended reporting category for the change.** For example, a type of process change, with a recommended filing category of a supplement--changes being effected in 30 days, could cause a new degradant to be formed that requires qualification and/or identification. However, the applicant's degradation qualification procedures may indicate that there are no safety concerns relating to the new degradant. The applicant should submit this change in a prior approval supplement with appropriate information to support the continued safety and effectiveness of the product. The FDA will assess the impact of any adverse effect on a product as it may relate to the safety or effectiveness of the product during the review of the prior approval supplement.

An applicant is encouraged to consult with the appropriate CDER chemistry or microbiology review staff if it has any questions on whether a change in a characteristic would be viewed by CDER as adversely affecting the identity, strength, quality, purity, or potency of the product.

V. COMPONENTS AND COMPOSITION

Changes in the qualitative or quantitative formulation, including inactive ingredients, as provided in the approved application are considered major changes and should be filed in a prior approval supplement, unless exempted by regulation or guidance (21 CFR 314.70(b)(2)(i)). The deletion or reduction of an ingredient intended to affect only the color of a product may be reported in an annual report (21 CFR 314.70(d)(2)(ii)). Guidance on changes in components and composition that may be filed in a changes being effected supplement or annual report is not included in this document because of the complexity of these recommendations, but may be covered in one or more guidance documents describing postapproval changes (e.g., SUPAC documents).

VI. SITES

A. General Considerations

Changes in sites for which FDA should be notified include those facilities or establishments used to (1) manufacture or process drug products,[7] in-process materials, drug substances or drug substance intermediates, (2) package drug products, (3) label drug products, and (4) test components, drug product containers, closures, packaging materials, in-process materials, or drug products. Testing facilities include those performing physical, chemical, biological, and microbiological testing to monitor, accept, or reject materials as well as those performing stability testing. Facilities used to label drug products are considered those that perform labeling of the drug product's primary or secondary packaging components. Facilities performing operations that place identifying information on the dosage form itself (e.g., ink imprint on a filled capsule) are considered to be facilities that manufacture or process the drug product. Sites include those owned by the applicant or contract facilities. The supplement or annual report should identify whether the proposed site is an alternative or replacement to those provided for in the approved application.

A move to a site that is routinely subject to FDA inspection, should be filed as a prior

[7] Manufacturing or processing drug product would also include the preparation (e.g., sterilization) of container closure systems.

approval supplement if (1) the facility has never been inspected by FDA for the type of operation that is being moved to that facility, (2) the type of operation used to be performed at the facility but at some time it had been discontinued and is now being restarted, or (3) the facility does not have a satisfactory CGMP inspection[8] for the type of operation being moved. A prior approval supplement also should be submitted if the manufacturing process at the new or refurbished facility will differ materially from that described in the approved application. Under these circumstances, a change involving a move to a new site or a refurbished site is considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

For labeling, secondary packaging and testing site changes, the potential for adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product is considered to be independent of the type of drug product dosage form or specific type of operation being performed. Therefore, the recommended reporting category for any one of these site changes will be the same for all types of drug products and operations. For sites used to (1) manufacture or process drug products, in-process materials, drug substances, or drug substance intermediates or (2) perform primary packaging operations, the potential for adverse impact and, consequently, the recommended reporting category depends on various factors such as the type of product and operation being performed. For this reason, recommended reporting categories may differ depending on the type of drug product and operations.
Factors used to assess whether a change in a site that manufactures or processes drug products, in-process materials, drug substances or drug substance intermediates or performs primary packaging operations is considered major include whether (1) the formulation and/or primary packaging components of the drug product control (or modify) the dose delivered to the patient and as a result the bioavailability of the product or (2) the production process involves certain technology (e.g., aseptic processing).

In general, the recommended reporting category for the primary packaging site of the drug product is the same as that for the manufacturing or processing site of the drug product. However, for certain products where a prior approval supplement is recommended for the drug product manufacturing or processing site, a supplement -- changes being effected in 30 days may be recommended for the primary packaging facility.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product

[8] Information on what constitutes a satisfactory CGMP inspection is provided in the glossary.

as they may relate to the safety or effectiveness of the product.

1. A move to any site, except one used to manufacture or process a drug substance intermediate, when the new facility has never been inspected by FDA for the type of operation that is being moved or the type of operation being moved used to be performed at the new facility, but at some time it had been discontinued and is now being restarted.

2. A move to a site, except those used to manufacture or process a drug substance intermediate, when the new facility does not have a satisfactory CGMP inspection for the type of operation being moved.

3. A move to a new site or refurbishing of an existing site where the operation being performed will differ materially from that described in the approved application. For example: (1) changes in the synthesis of a drug substance, (2) changes that could affect contamination or cross contamination precautions, (3) changing methods of sterilization or microbiological controls.

4. A move to a site on a different campus for the manufacture or processing of (1) drug products when the formulation and/or primary packaging components of the drug product control (or modify) the dose delivered to the patient or (2) in-process materials with modified release characteristics. Examples of these types of drug products include modified release solid oral dosage forms, transdermal systems, liposomal products, oral and nasal metered dose inhalers (MDIs), dry powder inhalers (DPIs), and nasal spray pumps.

5. Transfer of manufacturing of an aseptically processed sterile drug substance or sterile drug product to a newly constructed, refurbished, or different aseptic processing facility. Once this change has been approved, subsequent site changes to the facility for similar product types and processes may be filed as a supplement -- changes being effected in 30 days.

6. Except for modified release solid oral dosage form products, a move to a site on a different campus for the primary packaging of a drug product that falls within the scope of examples 4 or 5 (above).

C. Moderate Changes (Supplement--Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Supplement--Changes Being Effected in 30 Days

   a. A move to a site on a different campus for the manufacture or processing of any drug product, in-process material or drug substance that is not otherwise listed as a major change.

   b. A move to a site on the same campus (e.g., building changes) or within a single facility (e.g., room changes) for the manufacture or processing of sterile drug substance or drug product that is not otherwise listed as a major change.

   c. A move to a site on a different campus for the primary packaging of any drug product that is not otherwise listed as a major change.

   d. A move to a testing facility on a different campus if (1) the test procedure(s) approved in the application or procedures that have been implemented under 21 CFR 314.70(d) are used, (2) all postapproval commitments made by the applicant relating to the test procedure(s) have been fulfilled (e.g., providing methods validation samples), and (3) the new testing facility has the capability to perform the intended testing.

2. Supplement--Changes Being Effected

   a. A move to a new site on the same or different campus for the manufacturing or processing of the final intermediate.

   b. A move to a new site on the same or different campus for the manufacturing or processing of drug substance intermediates when the new site is owned by a contract manufacturer not previously approved for the application, or approved in the application but not approved for the manufacturing step(s) being transferred.

D. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as

they may relate to the safety or effectiveness of the product.

1. A move to a new secondary packaging site on the same (i.e., contiguous) or different campus.

2. A move to a new labeling site on the same or different campus.

3. A move to a new testing site on the same campus.

4. A move to a site on the same campus (i.e., building changes) for the manufacture or processing (including primary packaging) of nonsterile drug substance, in-process material, or drug product, except as otherwise listed.

5. Site changes within a single facility (e.g., room changes) for the manufacture or processing of drug product or in-process material, or primary packaging, except as otherwise listed for sterile drug products.[9]

6. A move to a new site on the same or different campus to manufacture or process drug substance intermediates, other than the final intermediate, when the new site is owned either by the applicant or by a contract manufacturer previously approved in the application for the manufacturing step(s) being transferred.

7. A change in the simple floor plan that does not affect the production process or contamination precautions. This includes a facility "build-out."

8. Improvements to manufacturing areas that provide greater assurance of quality.

9. Change in the contract sterilization site for packaging components when the process is not materially different from that provided for in the approved application and the facility has a satisfactory CGMP inspection for the type of operation being performed.

[9] Site changes within a single facility for the manufacture or processing of drug substance or drug substance intermediates need not be filed with the Agency, except as otherwise noted for sterile drug substances. However, installation qualification (IQ) and operation qualification (OQ) information should be retained in-house and is subject to FDA's review at its discretion.

VII. MANUFACTURING PROCESS

A. General Considerations

The potential for adverse effects on the identity, strength, quality, purity, or potency of a drug product as they may relate to the safety or effectiveness of the product depends on the type of manufacturing process and the changes being instituted for the drug substance or drug product. In some cases, there is a substantial potential for adverse effects, regardless of whether the applicant has determined that there has been no effect on the quality of the drug substance or drug product. This potential exists because the testing performed by the applicant to demonstrate the quality of the product may not be adequate or an important test may not have been performed to rule out such adverse effects. When there is a substantial potential for adverse effects, a change should be filed in a prior approval supplement. CDER considers that there is a substantial potential for adverse effects relating to a manufacturing process change when (1) changes may affect the controlled (or modified) release, metering or other characteristics (e.g., particle size) of the dose delivered to the patient and as a result the bioavailability of the product, (2) changes may affect product sterility assurance, (3) the production process involves certain technologies (e.g., certain production aspects for natural products),[10] (4) fundamental changes are made in the process or technology from that currently used, and (5) certain changes in drug substance manufacture.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Changes that may affect the controlled (or modified) release, metering or other characteristics (e.g., particle size) of the dose delivered to the patient including the addition of a code imprint by embossing, debossing, or engraving on a modified release solid oral dosage form.

2. Changes that may affect product sterility assurance including, where appropriate, process changes for sterile drug substances and sterile packaging components. These include:

[10] For the purposes of this guidance, *natural product* refers to products such as those derived from plants, animals, or microorganisms. The specific recommendations for natural products are not applicable to inorganic compounds (e.g., salts, minerals).

- Changes in the sterilization method(s).
- Addition, deletion, or substitution of steps in an aseptic processing operation.
- Replacing sterilizers which operate by one set of principles with sterilizers that operate by another principle (e.g., substituting gravity displacement steam autoclaves with autoclaves using superheated water spray).
- New equipment added to an aseptic processing line and made of different materials that come in contact with sterilized bulk solution or sterile drug components, or deletion of equipment from an aseptic processing line.
- Replacing a Class 100 aseptic fill area with a barrier system for aseptic filling.
- Replacement or addition of lyophilization equipment of a different size, that uses different operating parameters or lengthens the overall process time.
- Changes from bioburden based terminal sterilization to the use of an overkill process, and vice versa.
- Changes to aseptic processing methods, including scale, that extend the filling time into additional aseptic filling shifts or increases bulk solution storage time by more than 50 percent beyond the validated limits in the approved application.
- Changes in scale of manufacturing for terminally sterilized products that increase the bulk solution storage time by more than 50 percent beyond the validated limits in the approved application.
- Changes in sterilizer load configurations that are outside the range of previously validated loads.
- Changes to filtration parameters (including filter materials or filter size) requiring new validation studies for the new parameters.

3. The following changes for a natural product:

- Changes in the virus or adventitious agent removal or inactivation method(s).
- Changes in the source material (e.g., microorganism, plant) or cell line.
- Establishment of a new master cell bank or seed.

4. Any fundamental change in the manufacturing process or technology from that which is currently used by the applicant. For example:

- Dry to wet granulation or vice versa.
- Change from one type of drying process to another (e.g., oven tray, fluid bed, microwave).
- Filtration to centrifugation or vice versa.
- Change in the route of synthesis of a drug substance.

5. The following changes for drug substance:

   - Any process change made after the final intermediate processing step in drug substance manufacture.
   - Changes in the synthesis or manufacture of the drug substance that may affect its impurity profile and/or the physical, chemical, or biological properties.

6. Addition of an ink code imprint or change in the ink used for an existing imprint code for a solid oral dosage form drug product when the ink is not currently used on CDER-approved products.

7. Establishing a new procedure for reprocessing a batch of drug product that fails to meet the approved specification.

C. Moderate Changes (Supplement--Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Supplement--Changes Being Effected in 30 Days

   a. Any change in the process, process parameters and/or equipment, except as otherwise noted.

   b. For sterile products, drug substances and components, as appropriate:

      - Changes in dry heat depyrogenation processes for glass container systems for products that are produced by terminal sterilization processes or aseptic processing.
      - Changes to filtration parameters (such as flow rate, pressure, time, or volume, but not filter materials or size) that require additional validation studies for the new

parameters.

- Filtration process changes that provide for a change from single to dual product sterilizing filters, or for repeated filtration of a bulk.
- Elimination of in-process filtration performed as part of the manufacture of a terminally sterilized product.
- Changes from one qualified sterilization chamber to another for in-process or terminal sterilization that results in changes to validated operating parameters (time, temperature, F_0, and others). When terminal sterilization autoclaves are replaced, the range of thermal input (F-value) for the load should be demonstrated to fall within the range previously validated, such that the minimum thermal input does not reduce sterility assurance and the maximum thermal input does not reduce product stability or adversely affect container and closure integrity.
- Changes in scale of manufacturing for aseptically processed products that do not require additional aseptic filling shifts or do not increase bulk solution storage time by more than 50 percent beyond the validated limits in the approved application.
- Changes in scale of manufacturing for terminally sterilized products that increase the bulk solution storage time by no more than 50 percent beyond the validated limits in the approved application.

c. For drug substances, redefinition of an intermediate, excluding the final intermediate, as a starting material.

d. For natural protein products:

- An increase or decrease in production scale during finishing steps that involves new or different equipment.
- Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters.

2. Supplement--Changes Being Effected

No changes have been identified.

D. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Changes to equipment of the same design and operating principle and/or changes in scale, except as otherwise noted.

2. A minor change in an existing code imprint for a dosage form. For example, changing from a numeric to alphanumeric code.

3. To add an ink code imprint or to change the ink used in an existing code imprint for a solid oral dosage form drug product when the ink is currently used on CDER-approved products.

4. To add a code imprint by embossing, debossing, or engraving on a solid dosage form drug product other than a modified release dosage form.

5. A change in the order of addition of ingredients for solution dosage forms.

VIII. SPECIFICATIONS

A. General Considerations

All changes in specifications from those in the approved application must be submitted in a prior approval supplement unless otherwise exempted by regulation or guidance (21 CFR 314.70(b)(2)(i)). A *specification* is the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components including container and closure systems, and in-process materials. For the purpose of defining specification in 21 CFR 314.70, *acceptance criteria* are numerical limits, ranges, or other criteria for the tests described. The recommendations in this section also apply to specifications associated with monitoring of the production environment (e.g., environmental monitoring for particulates and/or microorganisms) that are included in NDA and ANDA submissions.

A regulatory analytical procedure is the analytical procedure proposed by the applicant and approved by FDA for evaluation of a defined characteristic of the drug substance or drug product. The analytical procedures in the *U.S. Pharmacopeia/National Formulary*

(USP/NF) are those legally recognized under section 501(b) of the Act as the regulatory analytical procedures for compendial items. The applicant may include in its application alternative procedures to the approved regulatory procedure for testing the drug substance and drug product. However, for purposes of determining compliance with the Act, the regulatory analytical procedure is used.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Relaxing an acceptance criterion, except as otherwise listed.

2. Deleting a test, except as otherwise listed.

3. Establishing a new regulatory analytical procedure.

4. Deleting a regulatory analytical procedure.

5. A change in a regulatory analytical procedure for drug substance or drug product or an analytical procedure used for testing components, packaging components, the final intermediate, or starting material(s) introduced after the final intermediate that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, except as otherwise noted. For example, a change from an HPLC procedure that distinguishes impurities to (1) one that does not, (2) another type of analytical procedure (e.g., titrimetric) that does not, or (3) one that distinguishes impurities but the limit of detection and/or limit of quantitation is higher.

C. Moderate Changes (Supplement--Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Supplement--Changes Being Effected in 30 Days

   a. Any changes in a regulatory analytical procedure other than those

identified as major changes.

b. Relaxing an acceptance criterion or deleting a test for raw materials used in drug substance manufacturing, starting materials introduced prior to the final drug substance intermediate, or drug substance intermediates (excluding final intermediate).[11]

c. A change in an analytical procedure used for testing raw materials used in drug substance manufacturing, starting materials introduced prior to the final drug substance intermediate, or drug substance intermediates (excluding final intermediate) that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

d. A change in an analytical procedure used for testing components, packaging components, the final intermediate, or starting materials introduced after the final intermediate that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

2. Supplement--Changes Being Effected

a. An addition to a specification or changes in methods or controls to provide increased assurance that the drug will have the characteristics of identity, strength, purity, or potency which it purports or is represented to possess. For example, adding a new test and associated analytical procedure and acceptance criterion.

D. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Any change made to comply with an official compendium that is consistent

[11] For raw material changes discussed in VIII.C.1.b and c, if changes can be justified without the need to generate test data, then filing in an annual report may be appropriate. In those situations, the appropriate chemistry review staff should be contacted for concurrence.

with FDA requirements and that provides the same or greater level of assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

2. For drug product and drug substance, the addition, deletion or revision of an alternative analytical procedure that provides the same or greater level of assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

3. Tightening of acceptance criteria.

4. A change in an analytical procedure used for testing raw materials used in drug substance synthesis, starting materials introduced prior to the final drug substance intermediate, or drug substance intermediates (excluding final intermediate) that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

5. Tightening of specifications for existing reference standards to provide increased assurance of product purity and potency.

IX. PACKAGE

A. General Considerations

The potential for adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product for a change in a package depends on the type of product and the functionality of the packaging. In some cases there is a substantial potential for adverse effect regardless of whether the applicant has determined that there has been no effect on the quality of the final product. This potential exists because the testing performed by the applicant to demonstrate the quality of the product may not be adequate or an important test may not have been performed to rule out such adverse effects. When there is a substantial potential for adverse effects, a change should be filed in a prior approval supplement. CDER considers the following package changes to have a substantial potential for adverse effects: (1) new plastics or rubbers are used in the primary packaging components of liquid dosage form products and the material has never been approved by CDER for use with that particular liquid dosage form; (2) new inks and/or adhesives are used on permeable or semipermeable container

closure systems and the ink and/or adhesive has never been approved by CDER for use with that particular liquid dosage form and type of container closure system; (3) the primary packaging components of the drug product control (or modify) the dose delivered to the patient and hence the bioavailability of the product; (4) changes may affect product sterility assurance; and (5) deletion of a secondary packaging component that is intended to provide additional protection to the drug product.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms, a change to or in polymeric materials (e.g., plastic, rubber) of primary packaging components, when the composition of the component as changed has never been approved by CDER for use with that particular liquid dosage form or semisolid dosage form.

2. Where ink and/or adhesive is used on a semipermeable or permeable container closure system a change to an ink and/or adhesive that has never been approved by CDER for use with that particular liquid or semisolid dosage form and type of permeable or semipermeable packaging component (e.g., low density polyethylene, polyvinyl chloride).

3. A change in the primary packaging components for any product where the primary packaging components control (or modify) the dose delivered to the patient.

4. For sterile products, any other change that may affect product sterility assurance such as:[12]

   - A change from a glass ampule to a glass vial with an elastomeric closure.
   - A change to a flexible container system (bag) from another container system.
   - A change to a prefilled syringe dosage form from another container system.

[12] Some of these identified changes, depending on the circumstances, may have to be filed as a new NDA or ANDA. An applicant should consult the appropriate CDER chemistry division/office if it has any questions.

- A change from a single unit dose container to a multiple dose container system.
- Changes that add or delete silicone treatments to container closure systems (such as elastomeric closures or syringe barrels).
- Changes in the size and/or shape of a container for a sterile drug substance or sterile drug product.

5. Deletion of a secondary packaging component that is intended to provide additional protection to the drug product.

C. Moderate Changes (Supplement--Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Supplement--Changes Being Effected in 30 Days

   a. A change in primary or secondary packaging components, except as otherwise listed.

2. Supplement--Changes Being Effected

   a. A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms.

D. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. A change in the container closure system for a nonsterile drug product, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium.

2. A change in the size and/or shape of a container containing the same number of dose units, for a nonsterile solid dosage form.

3. The following changes in the container closure system of solid oral dosage

form products as long as the new package provides the same or better protective properties (e.g., light, moisture) and any new primary packaging component materials have been used in and been in contact with CDER-approved solid oral dosage form products:[13]

- Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap.
- Changing from one plastic container to another of the same type of plastic (e.g., high density polyethylene (HDPE) to HDPE).
- Changes in packaging materials used to control odor (e.g., charcoal packets).
- Changes in bottle filler (e.g., change in weight of cotton or amount used) without changes in the type of filler (e.g., cotton to rayon).
- Increasing the wall thickness of the container.
- A change in or addition of a cap liner.
- A change in or addition of a seal (e.g., heat induction seal).
- A change in an antioxidant, stabilizer or mold releasing agent for production of the container and/or closure to one that is used at similar levels in the packaging of CDER-approved solid oral dosage form products.

4. The following changes in the container closure system of nonsterile liquid oral and topical dosage form products as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved liquid oral or topical dosage form products, as appropriate (i.e., the material in contact with a liquid topical should already be used in CDER-approved liquid topical products):

- Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap.
- Increasing the wall thickness of the container.
- A change in or addition of a cap liner.
- A change in or addition of a seal (e.g., heat induction seal).

5. A change in the container closure system of unit dose packaging (e.g., blister packs) for nonsterile solid dosage form products as long as the new

[13] For sections IX.D.3 to 6, changes in the container closure system that result in product contact with a component material that has never been used in any CDER-approved product of the same type should be filed as supplement — changes being effected in 30 days (IX.C.1) or prior approval supplement (IX.B.1).

package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved products of the same type (e.g., solid oral dosage form, rectal suppository).

6. The following changes in the container closure system of nonsterile semisolid products as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved semisolid products:

   - Changes in the closure or cap.
   - Increasing the wall thickness of the container.
   - A change in or addition of a cap liner.

7. Changes in secondary packaging components when the secondary packaging components are not intended to provide additional protection to the drug product.

X. LABELING

A. General Considerations

A labeling change includes changes in the package insert, package labeling, or container label. An applicant must promptly revise all promotional labeling and drug advertising to make it consistent with any labeling change implemented in accordance with the regulations (21 CFR 314.70(a)(4)). All labeling changes for ANDA products must be consistent with section 505(j) of the Act.

B. Major Changes (Prior Approval Supplement)

Under 21 CFR 314.70(b)(2)(v), any proposed change in the labeling, except those that are designated as moderate or minor changes by regulation (21 CFR 314.70(c) or (d)) or guidance, is required to be submitted as a prior approval supplement. The following list contains some examples of changes that are currently considered by CDER to fall into this reporting category.

1. Changes based on postmarketing study results, including, but not limited to, labeling changes associated with new indications and usage.

2. Change in, or addition of, pharmacoeconomic claims based on clinical studies.

3. Changes to the clinical pharmacology or the clinical study section reflecting new or modified data.

4. Changes based on data from preclinical studies.

5. Revision (expansion or contraction) of population based on data.

6. Claims of superiority to another product.

7. Change in the labeled storage conditions, unless exempted by regulation or guidance.

C. Moderate Changes (Supplement--Changes Being Effected)

Under 21 CFR 314.70(c)(6)(iii), a changes being effected supplement must be submitted for any labeling change that (1) adds or strengthens a contraindication, warning, precaution, or adverse reaction, (2) adds or strengthens a statement about drug abuse, dependence, psychological effect, or overdosage, (3) adds or strengthens an instruction about dosage and administration that is intended to increase the safe use of the product, (4) deletes false, misleading, or unsupported indications for use or claims for effectiveness, or (5) is specifically requested by FDA. The submission should include 12 copies of final printed labeling. The following list includes some examples of changes that are currently considered by CDER to fall into this reporting category.

1. Addition of an adverse event due to information reported to the applicant or Agency.

2. Addition of a precaution arising out of a post-marketing study.

3. Clarification of the administration statement to ensure proper administration of the product.

4. Labeling changes, normally classified as major changes, that FDA specifically requests be implemented using a changes being effected supplement.

D. Minor Changes (Annual Report)

Under 21 CFR 314.70(d)(2)(ix) and (x), labeling with editorial or similar minor changes or with a change in the information concerning the description of the drug product or information about how the drug is supplied that does not involve a change in the dosage strength or dosage form must be described in an annual report. The following list includes some examples that are currently considered by CDER to fall into this reporting category.

1. Changes in the layout of the package or container label that are consistent with FDA regulations (e.g., 21 CFR part 201), without a change in content of the labeling.

2. Editorial changes such as adding a distributor's name.

3. Foreign language versions of the labeling, if no change is made to the content of the approved labeling and a certified translation is included.

XI. MISCELLANEOUS CHANGES

A. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. Changes requiring completion of studies in accordance with 21 CFR part 320 to demonstrate equivalence of the drug to the drug as manufactured without the change or reference listed drug (21 CFR 314.70(b)(2)(ii)).

2. Changes that may affect product sterility assurance (21 CFR 314.70(b)(2)(iii)).

3. Approval of a comparability protocol (21 CFR 314.70(e)).

4. Extension of the expiration dating period of the drug product based on data obtained under a new or revised stability testing protocol that has not been approved in the application or based on pilot scale batch data.

5. Changes to an approved stability protocol or comparability protocol (21 CFR 314.70(e)) unless otherwise listed.

B. Moderate Changes (Supplement--Changes Being Effected)

No changes have been identified.

C. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

1. An extension of an expiration dating period based upon full shelf-life data on full production batches obtained from a protocol approved in the application (21 CFR 314.70(d)(2)(vi)).

2. Addition of time points to the stability protocol.

3. Reference standards:

   - Replacement of an in-house reference standard or reference panel (or panel member) according to procedures in an approved application.
   - Tightening of specifications for existing reference standards to provide greater assurance of product purity and potency.

XII. MULTIPLE CHANGES

Multiple changes involve various combinations of related changes. For example a site change may also involve equipment and manufacturing process changes or a components and composition change may necessitate a change in a specification. For multiple related changes, FDA recommends that the filing be in accordance with the most restrictive of those recommended for the individual changes.

GLOSSARY OF TERMS

Acceptance Criteria: Numerical limits, ranges, or other criteria for the tests described (21 CFR 314.3).

Active Ingredient/Drug Substance: Any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient. The term includes those components that may undergo chemical change in the manufacture of the drug product and are present in the drug product in a modified form intended to furnish the specified activity or effect (21 CFR 210.3(b)(7) and 314.3).

Container Closure System: The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product.

Contiguous Campus: Continuous or unbroken site or a set of buildings in adjacent city blocks.

Component: Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product (21 CFR 210.3(b)(3)).

Drug Product: A finished dosage form, for example, tablet, capsule or solution, that contains an active ingredient, generally, but not necessarily, in association with inactive ingredients (21 CFR 210.3(b)(4)).

Final Intermediate: The last compound synthesized before the reaction that produces the drug substance. The final step forming the drug substance must involve covalent bond formation; ionic bond formation (i.e., making the salt of a compound) does not qualify. Consequently, when the drug substance is a salt, the precursors to the organic acid or base, rather than the acid or base itself, should be considered the final intermediate.

Inactive Ingredients: Any intended component of the drug product other than an active ingredient.

In-process Material: Any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product (21 CFR 210.3(b)(9)).

Intermediate: A material produced during steps of the synthesis of a drug substance that must undergo further molecular change before it becomes a drug substance.

Installation Qualification (IQ): The documented verification that all key aspects of the equipment and ancillary systems installations adhere to the approved design intentions (plans) and that the recommendations of the manufacturer are suitably considered.

Operational Qualification (OQ): The documented verification that the equipment and ancillary systems perform as intended throughout anticipated operating ranges (i.e., pressures, temperatures, times).

Package: Refers to the container closure system and labeling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons, shrink wrap).

Packaging Component: Any single part of a container closure system.

Primary Packaging Component: A packaging component that is or may be in direct contact with the dosage form.

Reference Listed Drug: The listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application (21 CFR 314.3).

Satisfactory Current Good Manufacturing Practice (CGMP) Inspection: A satisfactory CGMP inspection is one during which (1) no objectionable conditions or practices were found during an FDA inspection (No Action Indicated (NAI)) or (2) objectionable conditions were found, but, corrective action is left to the firm to take voluntarily and the objectionable conditions will not be the subject of further administrative or regulatory actions (Voluntary Action Indicated (VAI)).

Information about the CGMP status of a firm may be obtained by requesting a copy of the Quality Assurance Profile (QAP) from the FDA's Freedom of Information (FOI) Office. The QAP reports information on the CGMP compliance status of firms which manufacture, package, assemble, repack, relabel or test human drugs, devices, biologics and veterinary drugs. All FOI requests must be in writing and should follow the instructions found in the reference entitled *A Handbook for Requesting Information and Records from FDA*. An electronic version of this reference is available on the Internet at http://www.fda.gov/opacom/backgrounders/foiahand.html.

Secondary Packaging Component: A packaging component that is not and will not be in direct contact with the dosage form.

Specification: The quality standard (i.e., tests, analytical procedures, and acceptance criteria)

provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components including container closure systems, and in-process materials (21 CFR 314.3).

Validate the Effects of the Change: To assess the effect of a manufacturing change on the identity, strength, quality, purity, or potency of a drug as these factors relate to the safety or effectiveness of the drug (21 CFR 314.3).